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Attn: Section 8(e) Coordinator
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Gentlemen:

Phillips Petroleum Company is submitting the enclosed sixty (60) reports (two boxes, numbered 1 and 2) of toxicological studies pursuant to catagory II.B.2.b of the CAP Agreement 8ECAP-0075 Reports. Reports being submitted contain no confidential business information.

We are sending an additional five boxes (box numbers 3-7) of reports of studies that have, previously, been submitted to the FYI coordinator of the Office of Pollution Prevention and Toxics by the American Petroleum Institute (API). These are being provided solely for the Agency's convenience.

For questions concerning this correspondence, plese contact Fred Marashi at 918-661-8153.

Very truly yours,

Barbara J. Price

Barbara J. Price
Vice President
Health, Environment & Safety

Enclosure (Seven Boxes)

FFM/dh:29

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Phillips Petroleum Company

CAP Identification Number: 8ECAP-0075
Pursuant to Category: II.B.2.b

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Title of Study: Chronic Benzene Toxicology

Name of Chemical: Benzene

CAS#: 71-43-2

Summary: Rodents exposed chronically to benzene exhibited lymphoma, leukemia and other blood changes.

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FINAL REPORT

To the American Petroleum Institute
Washington, D.C.

CHRONIC BENZENE TOXICOLOGY

Project U-150-14 (PS-7)

Principal Investigators: Sidney Laskin and Bernard Goldstein

From the Institute of Environmental Medicine
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New York, NY 10016

August 22, 1978

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Introduction

The rationale of this study was to develop suitable animal models for benzene-induced hematopoietic toxicity. The study was essentially divided into three sections or phases. Phase I was a comprehensive literature review which served as a basis for the direction of research and which was summarized in a monograph. Phase II included the toxicity studies of inhaled benzene and was divided into three areas. Area A was concerned with the inhalation protocols and peripheral blood cell monitoring. Area B dealt with the evaluation of hematological responses other than peripheral cell counts. Area C concerned the effects of benzene exposure on proliferating blood cell precursors as reflected by changes in bone marrow cytogenetics and colony forming abilities. Phase III dealt with the study of the metabolism of benzene which was investigated through pharmacokinetic techniques.

Phase I - Literature Review

Over 1000 pertinent articles were critically reviewed and catalogued. A monograph based on this review was published in November, 1977 as a supplement to the Journal of Toxicology and Environmental Health.[1]

Phase II - Toxicity

Area A

Exposures were performed in identical inhalation units ($1.6m^3$ total volume). Chamber atmospheres were sampled every 0.5 hours or 12 times during the daily runs. For most studies treated animals received either 300 ppm or 100 ppm benzene vapor for 6 hr/d x 5 d/wk x life. Air sham controls were exposed analogously to filtered, conditioned air. When not in the inhalation units rats were housed two to a cage and fed food and water ad libitum. Mice were housed five to a cage in polycarbonate boxes and allowed food and water ad libitum. Animals received neither food nor water during exposures. The numbers of animals used in each study and calculated median lifespans are shown in Table 1.

Animals were usually bled (by tail clipping) biweekly for determination of peripheral cell responses. Only males were used in order to avoid anomolous white counts due to estrus. Test and corresponding air sham animals were bled within one hour by the same individual in order to minimize differences in white counts due to handling, circadian rhythm, etc. Routinely, red blood counts, white blood counts and differential white blood counts were determined on all animals, but other parameters were frequently investigated including hematocrit, hemoglobin and reticulocyte levels.

Sprague-Dawley Rats at 300 ppm

The chronic exposure of Sprague-Dawley rats to 300 ppm benzene was completed at 99 weeks with the death of the last test animal. These animals received up to 463 exposures over the 691 days of the study at an integrated mean concentration of 301 ppm. The calculated median lifespan of the test animals was 59 weeks versus 73 weeks for the controls (Table 1). Test animals first showed weight depression when compared with controls at 30 weeks, and this trend continued throughout the study although weight differences were never greater than two standard errors ($\pm 2S_x$).

The acquisition of blood data was suspended after one year of exposure due to advancing mortality in test rats. Blood counts performed during the first year demonstrated that benzene induced significant ($\pm 2S_x$) leukopenia in test rats and that this leukopenia was due to a selective decrease in lymphocyte levels (Figure 1). Red cell counts for the first exposure year suggested a trend to anemia in test rats, however, differences in red cell levels between test and control animals were not as striking as differences in white cell levels (Table 2). An evalutation of the weekly red cell data shows that test animals had lower counts than controls in 69% (26/38) of the counts taken during the first exposure year. Consistent with the red cell counts, hematocrit and hemoglobin determinations showed no differences between test and control animals.

Evaluation of tissue sections revealed hemosiderin pigments in 42% of the spleens taken from test rats as opposed to 18% in the spleens of control animals. These results were shown not to be significant, however, at the p = 0.05 level by X^2 analysis. Fatty changes appeared in 77% of the bone marrows of test animals versus 42% for controls. Evaluation by X^2 showed these results to be significant at p = 0.05. No pathological differences were observed in the other organs studied.

AKR Mice at 300 ppm

The chronic exposure of AKR/J mice to 300 ppm benzene was completed after 28 weeks with the death of the last test animal. Treated mice received up to 123 exposures over the 181 days of the study at an integrated mean benzene concentration of 301 ppm.

Treated mice exhibited a median survival time of 17 weeks compared with a median survival time of 47 weeks for controls (Table 1). Weight data taken during the exposure showed severe weight loss for the treated versus the untreated mice (Table 3).

The monitoring of blood parameters was suspended after 92 days because of high mortality in the test mice. The blood data demonstrated that benzene induced severe lymphocytopenia in the exposed animals (Figure 2) but that these animals still retained an ability to produce granulocytes

during the exposure. Red cell data showed that benzene also induced anemia in test mice (Figure 3). Reticulocytosis first appeared concurrent with the development of anemia and became significant ($\pm 2S_x$) at 37 days exposure (Table 4).

Evidence of malignant lymphoma was found in tissue sectioned from 91% of the control mice but in only 2% of the exposed mice. The AKR strain spontaneously develops lymphoid leukemia at an incidence of 85-95%. The very low lymphoma incidence in treated mice was due to the severe rate of mortality induced by the exposure. The first lymphoma appeared after 6 months in the untreated mice whereas the median survival for treated mice was only 4 months.

Hemosiderin pigments were found in spleens taken from 25% of the treated mice while no pigment was detected in control mice. Chi square analysis showed these differences to be significant at the $p < 0.001$ level.

Bone marrow hypoplasia was exhibited by 81% of the exposed mice but by only 6% of the controls. This, also, was found to be significant at the $p < 0.001$ level by X^2 analysis. Several test mice exhibited bone marrow hypoplasia of such severe proportions that only isolated nests of hematopoietic tissue were present in an otherwise empty marrow.

C-57 Bl Mice at 300 ppm

The chronic exposure to C-57 Bl mice was completed after 488 days with the death of the last test animal.

During the exposure period, test mice received 331 exposures at an integrated mean concentration of 300 ppm.

Treated mice exhibited a median survival time of 49 weeks versus 83 weeks for controls (Table 1) and showed weight gain depression relative to controls throughout the study.

Acquisition of peripheral blood data was suspended after 61 weeks due to advancing mortality in test mice.

Test mice exhibited statistically significant lymphocytopenia and anemia relative to controls after one exposure week and this trend continued throughout the course of the study (Table 5). Granulocytosis was evident in test mice vis a vis controls after 17 weeks and was statistically significant during most of the remainder of the exposure (Table 5).

Malignant lymphoma was detected in 9/40 treated animals but in only 2/40 controls. This is a statistically significant increase in the treated animals at the $p < 0.05$ level as shown by X^2 analysis. Because C-57 Bl mice carry a radiation-inducible lymphoma virus,[2] the observed increased incidence of lymphoma may indicate similar modes of action for benzene and ionizing radiation. Six of the test mice presented hypoplastic bone marrow. Four of these were associated with malignant lymphoma. No control mice gave evidence of bone marrow hypoplasia.

Of those test animals that did not show evidence of malignant lymphoma, 13/31 exhibited bone marrow hyperplasia and 15/31 exhibited spleen hyperplasia. These compared with no cases of bone marrow hyperplasia and 2/38 cases of spleen hyperplasia in the controls.

Charles River CD-1 Mice at 300 ppm

The exposure of CD-1 mice to 300 ppm benzene ended after 222 days with the development of two cases of myelogenous leukemia. During the exposure period animals received 149 exposures at an integrated mean benzene concentration of 300 ppm. At the time exposure was suspended, 9 test animals remained alive. The last of these animals died 8 weeks later.

The calculated median survival time was 31 weeks for treated animals and 50 weeks for controls (Table 1). Treated animals showed a decreased rate of weight gain relative to controls throughout the exposure but the largest differences were noted from the twenty-eighth week onward.

The blood data presented below was compiled from all test and control animals with the exception of the two treated animals with myelogenous leukemia.

Treated animals exhibited statistically significant lymphocytopenia and anemia after one exposure week and this trend continued throughout the course of the study (Figures 4 and 5). At 25 weeks, treated mice began showing a steadily

increasing granulocytosis relative to controls which continued until the end of the study (Figure 4).

Histological evaluation of all animals is not yet complete, however, a summary of the findings for three mice presenting hematological and histological profiles of note is given below.

A mouse dying after 130 exposure showed a white count in excess of 160,000/mm^3 (control=12,000/mm^3). The peripheral smear showed a preponderance of granulocytes shifted to the left. Bone marrow, spleen and liver sections were perfused with myeloid cells and there was infiltration by these cells into the muscle and connective tissue surrounding the bone. Death was ascribed to chronic myelogenous leukemia.

A second mouse dying after 139 exposures showed a normal white count of 11,000/mm^3 but 30% of the cells were blasts. Other cells in the peripheral smear were granulocytic types shifted to the left. Masses of cells were observed replacing normal architecture in bone marrow and spleen. These cells were a mononuclear type of varying sizes and appeared to mature towards the granulocytic series. Death was ascribed to acute myelogenous leukemia. Originally there was some doubt as to the nature of the proliferating cell type in this case. The peripheral cell morphology could have been consistent with either stem cell leukemia or acute myelogenous leukemia. Since there is a 4% spontaneous incidence of stem cell leukemia associated with these mice,[3]

the question of cell type as it concerns benzene exposure was crucial. Review of pertinent slides by Drs. Arthur Upton and Albert Jonas (see enclosures) seems to confirm the myeloid nature of the proliferating cell. Dr. Jonas' diagnosis is particularly compelling since he has, to our knowledge, reviewed the largest colony of these animals.

In addition to the above cases, a CD-1 mouse dying after 222 exposures showed alternating elevated and normal white counts during successive monitorings. The peripheral smears showed granulocytes shifted to the left. The bone marrow was perfused with granulocytic cells and contained few other myelopoietic cell types. There was no invasion by these cells into the peripheral regions, however, nor was there any indication of ectopic granulopoiesis. For this reason, the animal was diagnosed with granulocytic hyperplasia which could be considered a pre-myelogenous leukemic state.

AKR Mice at 100 ppm

The chronic exposure study of these mice to 100 ppm benzene ended after 505 days with the death of the last test animal. Treated mice received 337 exposures at an integrated mean benzene concentration of 100 ppm. There appeared to be no differences between test and control mice in median survival or in rate of weight gain (Table 1).

Hematological monitoring was suspended after 37 weeks due to advancing mortality in test mice. Statistically

significant lymphocytopenia was observed in treated mice vs. controls after one exposure week and this trend continued throughout the exposure. Lymphocyte depressions, however, were not as severe as those observed in the 300 ppm study with these animals (Table 6). Red cell levels of treated animals were depressed relative to controls and these depressions were statistically significant ($\pm 2S_x$) for 9/20 monitorings (Table 6). Test mice showed a trend to granulocytosis throughout the exposure, however granulocyte levels were elevated by statistically significant amounts in only 3/20 monitorings.

Histological evaluation revealed few differences between test and control animals. Malignant lymphoma was confirmed in 29/49 treated animals and in 24/50 controls. The average lifespan of treated animals dying with malignant lymphoma was 247 days. The average lifespan for controls was 226 days. Bone marrow hypoplasia was found in 11 treated mice (22%) but in only one control. This compares with an 81% incidence of bone marrow hypoplasia found in these animals at 300 ppm.

Sprague-Dawley Rats at 100 ppm

The chronic exposure of these rats at 100 ppm is in progress with seventeen treated animals and nine controls still alive. Treated animals have received 428 exposures over 638 days at an integrated mean benzene concentration of 100 ppm.

Peripheral blood data indicates a trend in treated animals toward anemia and lymphocytopenia, however, the differences between test and control animals in red cell and lymphocyte levels has been rarely statistically significant ($\pm 2S_x$) (Table 7).

Histological evaluation of rats dying during the study has commenced. One treated rat has died with a confirmed chronic myelogenous leukemia. Details of the histological and hematological evaluation are as follows. The animal died after 233 exposures to 100 ppm benzene and showed a progressively increasing white count for several months before succumbing. The white count eventually rose to greater than 300,000/mm^3 (control=10,000/m^3). The peripheral smears showed marked increases in granulocytes shifted to the left. There was severe splenomegaly accompanied by an infarct which was visible at necropsy. The bone marrow was green and contained unsegmented granulocytes infiltrating into the periosteal regions. The liver, spleen, lymph nodes, and kidneys were perfused with myelopoietic elements. Death was ascribed to chronic myelogenous leukemia.

With the development of this case of chronic myelogenous leukemia, all treated and control rats have been screened monthly for hematologic abnormalities. To date, no control animals have presented signs consistent with leukemia. A second test rat has shown signs which may be consistent with the early stages of chronic myelogenous leukemia. White

counts have reached in excess of 100,000/mm^3 and a shift to the left has been observed. This animal now undergoes weekly hematologic monitoring.

Area B

Rats at 300 ppm

Because the red cell count data were equivocal for these animals at 300 ppm and because circulating cell counts are not necessarily good indicators of bone marrow toxicity, several additional red cell parameters were investigated at various times during the course of the chronic exposure.

Lactic dehydrogenase levels were monitored periodically from the twentieth week of exposure. Elevated levels were found in the test animals when compared with controls and the higher levels were significant ($\pm 2S_x$) for assays performed on the twenty-first, twenty-second and twenty-seventh weeks (Table 8). Assays performed subsequent to the twenty-seventh week still showed elevated levels for test animals, however, control animals also showed increased LDH levels.

Red cell osmotic fragility was determined during the eighteenth, twenty-ninth and thirty-first weeks of exposure. Initially test animals showed slightly increased fragility at 0.35% saline. Subsequent determinations, however, showed no significant difference between test and control animals.

Red cell glutathione levels assayed on the fifteenth and seventeenth week of exposure showed no significant

differences between test and control animals nor did red cell acetylcholinesterase levels monitored during the twenty-seventh and twenty-eighth week of exposure.

AKR Mice at 300 ppm and 100 ppm

Since lactic acid dehydrogenase levels were found to be elevated at times during the exposure of Sprague-Dawley rats to 300 ppm benzene, it was decided to modify L.D.H. procedures so that this parameter could be followed during the exposure of AKR mice to 300 ppm and 100 ppm benzene vapor. No significant differences were found in the L.D.H. levels of test and control animals at either exposure level. Red cell glutathione levels were lower in test mice exposed to 300 ppm, however this decrease seemed to parallel the red blood cell drop found in test animals and therefore may not have been due to decreased production of glutathione.

Area C

AKR Mice at 300 ppm and 100 ppm

Cytogenetic analyses were performed on femoral cells from AKR mice exposed to 300 ppm benzene and from air controls. Assays were taken regularly until the ninety-third exposure day. The results are summarized in Table 9.

The mitotic rate was lower in benzene-treated mice except for the last three data points. The number of euploid cells was higher in the controls at each point in the study.

In the latter half of the study after five weeks of exposure, there were more breaks observed in treated than in untreated animals. Although the direction of change was the same, a statistically significant increment within the animal pairs was only seen at 38 and 93 days ($p < 0.05$). Almost all breaks were open chromatid or chromosome breaks with the distal piece in geographic proximity to the parent chromosome, but with distal and lateral displacement. The breaks essentially followed the expected distribution for Poisson events with well over 90% of the cells in each series having only a single break.

A successful bone marrow cloning technique was developed using C-57 Bl and AKR mouse marrow cells. This procedure was applied on a regular basis to femoral marrow cells taken from AKR mice exposed to 100 ppm benzene. Although an initial depression in the number of colonies formed from benzene treated mice was noted, subsequent assays showed no differences in colony forming ability or cellularity (Table 10).

Phase III

Techniques were developed during the course of these studies for the determination of benzene in blood and tissue.[7,8] Application of these techniques demonstrated that benzene concentrates in the bone marrow during a single 6 hr exposure (Table 11). In addition, the results indicated a correlation

between various tissue concentrations and atmospheric concentrations.

Pharmacokinetic analyses were performed on the time-courses of benzene in the blood of animals exposed to benzene vapor. Because of the extreme differences in hematological responses elicited from Sprague-Dawley rats and AKR mice exposed to given levels of benzene, these animals were chosen as models for this study. Animals were given 20 exposures to either 300 ppm or 100 ppm benzene and pharmacokinetic analyses were performed after the first, sixth and twentieth exposures. Results show that the mice eliminated benzene faster than the rats for a given atmospheric concentration (Table 12). In addition, mice exposed to 300 ppm showed a shift from a monoxponential clearance to a biexponential clearance after the twentieth exposure at 300 ppm. Such a shift is theoretically possible but does not seem to have been observed previously. Mice also showed a trend to increasing rates of elimination at 300 ppm which is indicative of metabolic enzyme induction.

The comparative rates of elimination for these rats and mice correlates well with the observed hematotoxicity. AKR mice exhibited a much more severe toxic response to a given level of benzene than the rats and the rates of elimination for the mice were faster than the rates observed for rats at both levels of benzene studied. In addition, at 300 ppm, AKR mice showed a continuing drop in peripheral cell levels

up to and beyond 20 exposures and this correlates well with the increasing rates of elimination observed for these mice at 300 ppm.

Summary

1. Cytopenic effects of benzene exposure were readily produced in the animals chosen for study at 300 ppm. At this level, all animals exhibited peripheral lymphocytopenia and all of the mice studied exhibited anemia. Rats, on the other hand, showed lymphocytopenia but only a trend toward anemia. At 100 ppm AKR mice gave evidence of a dose-response effect in that the lymphocytopenia and anemia were not as marked as at the 300 ppm level. Rats at 100 ppm also showed a dose-response cytopenic effect by exhibiting only non-statistically significant trends to peripheral cell effects.

2. The pharmacokinetic data shows a direct relationship between the rate of clearance of benzene and benzene-induced cytopenia. This situation is the reverse of the usual relationship observed between toxicity and clearance rates. For most toxic compounds, a faster clearance rate usually causes a decrease in administered dose and therefore milder toxicity. Our toxicity data suggest that the faster clearance rates exhibited by the mice vis a vis the rats may not be a function of increased respiration rates alone but may also be due to increased metabolic rates which would lead to greater accumulation of toxic metabolites. This view is

further supported by the fact that the clearance rates and cytotoxicity for AKR mice at 300 ppm appear to increase with increasing exposure. It would be difficult to ascribe these increasing rates to increased respiration rates. A more reasonable explanation would seem to be metabolic enzyme induction with consequent increases in toxic metabolites.

3. All of the mouse strains studied responded to the exposures with granulocytoses. At times, test mice showed six-fold increases in granulocyte levels vis a vis controls. Often shifts to immature cell types accompanied these increased granulocyte levels. For the CD-1 mice, a spectrum of various stages of granulocyte proliferation was noted. In view of the observed cytopenic effects of benzene on the lymphoid and erythroid cell lines, the observed proliferative effect on the myeloid cell line seems all the more compelling. This is especially true in view of the correlation between benzene exposure and myelogenous leukemia in humans.

4. There were three confirmed cases of myelogenous leukemia among the test animals studied. In view of the small numbers of animals developing leukemia, these results must be considered preliminary. Although the number of controls used in these studies was relatively small, there have been, to our knowledge, no reports of spontaneous myelogenous leukemia in either CD-1 mice or Sprague-Dawley rats. These three cases of myelogenous leukemia, therefore, should be considered indicative of a causal relationship

between benzene exposure and myelogenous leukemia. Additional evidence for the carcinogenicity of benzene comes from the statistically significant increase in lymphoma among the C-57 Bl mice. Several known chemical carcinogens[6] as well as ionizing radiation produce a similar response in these mice.

5. The question of whether myelogenous leukemia follows episodes of peripheral cytopenia or arises without noticeable "preleukemic" peripheral cell changes must be considered as unanswered. The 2 mice developed leukemia after long episodes of peripheral anemia and lymphocytopenia whereas the rat showed peripheral cell counts within normal limits before presenting signs of myelogenous leukemia. It is possible that these varying responses represent species variability to a given toxic agent or they may have been due to varying individual responses. It is obvious that additional work should be conducted in this area.

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Table 1

Animal	Number at Risk	Exposure Level (ppm)	Calculated* Median Survival Time
Sprague-Dawley Rat	45	300	59 weeks
	27	0	73 weeks
Sprague-Dawley Rat	40	100	In progress
	40	0	
AKR Mouse	60	300	17 weeks
	60	0	47 weeks
AKR Mouse	49	100	39 weeks
	50	0	41 weeks
CD-1 Mouse	40	300	31 weeks
	40	0	50 weeks
C-57 Bl Mouse	40	300	49 weeks
	40	0	83 weeks

* The 50% survival point from least squares linear regression curve of log of survival vs. probability of mortality.

TABLE 2

COMPARISON OF RED BLOOD COUNTS BETWEEN SPRAGUE-DAWLEY RATS

EXPOSED TO 300 PPM BENZENE AND AIR CONTROLS

Weeks After First Exposure	Test $\pm 2S_{\bar{x}} \times 10^6$	Control $\pm 2S_{\bar{x}} \times 10^6$
4	16.00 ± 1.70	17.20 ± 2.90
8	9.83 ± 1.20	9.60 ± 0.80
12	8.35 ± 0.68	8.11 ± 0.62
16	3.51 ± 0.46	4.61 ± 0.66
20	7.88 ± 0.60	8.60 ± 0.32
24	10.11 ± 1.16	8.77 ± 0.76
28	7.83 ± 0.34	8.55 ± 0.74
32	8.47 ± 0.30	8.74 ± 0.32
35	7.61 ± 0.04	9.00 ± 0.46
40	9.28 ± 0.26	9.20 ± 0.10
44	10.25 ± 1.06	9.59 ± 0.40
48	9.64 ± 0.52	9.70 ± 0.30
52	8.37 ± 0.86	9.01 ± 0.38

TABLE 3

WEIGHT CHANGES OF AKR MICE EXPOSED TO 300 PPM

BENZENE AND AIR CONTROLS

Weeks After First Exposure	Percent Weight Change* Exposed Mice Initial Weight = 28.4 g	Percent Weight Change* Air Controls Initial Weight = 28.4 g
4	91	103
8	79	110
12	68	105
16	59	102
20	61	106
24	74	91
28	--	97
36	--	98
40	--	91
48	--	90
52	--	87

* Initial Weight Taken as 100%

TABLE 4

RETICULOCYTE COUNTS OF AKR MICE

EXPOSED TO 300 PPM BENZENE AND AIR CONTROLS

Days After 1st Exposure Day	Benzene % Retic ± $2S_x$	Control % Retic ± $2S_x$
0	7.4 ± 2.0	5.1 ± 1.8
9	6.0 ± 1.2	5.2 ± 1.8
23	2.2 ± 0.8	1.6 ± 0.4
37	3.3 ± 0.8	1.5 ± 0.2
65	3.2 ± 1.0	1.2 ± 0.2

Table 5

Comparison of Peripheral Blood Counts Between
C-57 31 Mice Exposed to 300 ppm and Air Control

Weeks After First Exposure	Test			Control		
	Lymphs	Polys	RBC	Lymphs	Polys	RBC
0	9100	1000	10.67	7600	1000	10.79
1	6600*	1200*	9.43*	11900	1900	10.64
9	4000*	3300	6.19*	12000	1800*	9.39
17	2300*	4100	6.63*	11500	2300	9.88
25	2000*	4800	6.95*	10000	2600*	9.65
33	3200*	3800	6.48*	10500	2000*	9.48
41	4600*	4500	6.29*	11800	2500	9.66
49	3800*	8300	6.26*	12100	2000*	9.57
57	2500*	7200	6.59*	14800	3200*	9.78

* denotes lower by a statistically significant difference (± 2 standard errors).

Table 6

Comparison of Peripheral Cell Counts Between AKR Mice Exposed to 100 ppm and Air Controls

Weeks After First Exposure	Test			Control		
	Lymphs	Polys	RBC	Lymphs	Polys	RBC
0	10400	3300	9.49	9400	2600	9.33
1	6700*	1700*	7.83*	9800	2900	8.83
5	3600*	3900	8.40*	9300	4400	9.06
9	3200*	4000	8.26*	10900	3600	9.07
13	2700*	2800	8.12*	8000	3100	8.88
17	3500*	5000	8.80	9500	2600*	9.18
21	2800*	6000	8.54	7100	2500*	9.18
25	2400*	5000	8.27	6800	3800	9.03
29	4200	4000	8.21	4500	3600	10.17
33	2800*	5100	8.56	7600	4300	9.82
37	2500*	7000	6.90*	7800	5100	8.14

* denotes lower by a statistically significant difference (± 2 standard errors).

Table 7

Comparison of Peripheral Blood Counts Between
Sprague-Dawley Rats Exposed to 100 ppm and Air Control

Weeks After First Exposure	Test			Control		
	Lymphs	Polys	RBC	Lymphs	Polys	RBC
0	14100	2500	6.59	13900	2900	6.98
8	12100	1400	7.50	11900	2400	7.57
16	9100	2000	7.70	11200	1900	8.09
24	9300	2200	7.67	10700	1300*	7.95
32	10600	2900	8.04	13800	3900	8.20
38	9900	2400	8.60	11400	2300	8.77
45	10300	2900	7.97	11900	3000	8.47
53	11300	3700	8.03	12700	4300	8.30
61	11200	3600*	7.68*	12000	6100	9.00
70	10621	5100	8.21	13200	5200	9.08
77	9000	4700	8.05	11800	5700	8.40

* denotes lower by a statistically significant difference (± 2 standard errors).

TABLE 8

COMPARISON OF LACTIC ACID DEHYDROGENASE LEVELS BETWEEN

SPRAGUE-DAWLEY RATS EXPOSED TO 300 PPM BENZENE AND AIR CONTROLS

Weeks After First Exposure	Controls In L.D.H. Units (C)	$2 S_x$	Exposed In L.D.H. Units (E)	$2 S_x$	Differences In L.D.H. Units (E - C)
20	570	270	860	270	+ 290
21	650	130	1410	300	+ 760
22	1000	310	1530	200	+ 530
27	270	70	1040	350	+ 770
28	530	120	940	300	+ 410
36	1110	490	1150	350	+ 40

TABLE 9

COMPARISON OF BONE MARROW CELLULAR MORPHOLOGY BETWEEN AKR MICE EXPOSED TO 300 PPM BENZENE AND AIR CONTROLS

Exposure	Duration of Exposure (Days)	Percent Diploid	Percent Hypodiploid	Percent Hypodiploid	Percent Cells With Breaks	Mitotic Rates
Pre-Exposure	--	90	9	1	5	1.8
Benzene	10	74	26	0	21	0.6
Air	--	91	7	2	16	0.8
Benzene	17	81	19	0	20	1.2
Air	--	86	13	1	21	2.0
Benzene	24	86	11	3	21	1.0
Air	--	93	7	0	30	2.0
Benzene	38	79	18	3	29	1.6
Air	--	96	4	0	16	2.0
Benzene	52	80	20	0	12	1.0
Air	--	92	5	3	8	1.0
Benzene	66	86	6	8	26	1.6
Air	--	92	8	0	21	1.2
Benzene	93	85	15	0	34	3.0
Air	--	91	9	0	16	1.6

TABLE 10

COMPARISON OF CELLULAR PROLIFERATIVE ABILITY OF BONE MARROWS CELLS

FROM AKR MICE EXPOSED TO 100 PPM BENZENE AND AIR CONTROLS

Weeks After First Exposure	Type of Exposure	Number of Colonies	Cellularity x 10^6
2	Benzene	1	15
	Benzene	5	19
	Air	35	28
	Air	21	20
6	Benzene	13	34
	Benzene	13	29
	Air	19	44
	Air	15	35
10	Benzene	2	28
	Benzene	2	30
	Air	2	30
	Air	4	20
12	Benzene	7	16
	Benzene	5	20
	Air	1	39
	Air	12	25

TABLE 11

BENZENE (C_6H_6) DISTRIBUTION IN HEMATOPOIETIC TISSUE OF AKR MICE EXPOSED TO BENZENE VAPOR FOR 6 HOURS

100 PPM

Mouse	Weight (g)	C_6H_6 Conc. in blood (µg/ml)	C_6H_6 Conc. in liver (µg/g)	C_6H_6 Conc. in spleen (µg/g)	C_6H_6 Conc. in marrow (µg/g)
1	27	2.22	17.58	2.50	3.58
2	33	3.21	7.10	1.55	5.85
3	30	8.47	13.67	2.07	1.71
4	36	1.81	10.55	0.43	24.34

300 PPM

5	29	13.98	53.69	2.38	11.40
6	29	11.51	90.41	6.70	41.35
7	34	9.29	57.00	19.61*	15.63
8	28	23.0	58.25	11.17	75.66

*Splenomegaly

Table 12

Comparison of Mean Elimination Rate Constants
Between Rats and Mice Exposed to Benzene Vapor

Concentration	Exposure 1st	6th	20th
300 ppm	$k_{m/k_r} = 4.3$	$k_{m/k_r} = 4.2$	$k_{m/k_r} = 7.0$
100 ppm	$k_{m/k_r} = 5.3$	$k_{m/k_r} = 3.4$	$k_{m/k_r} = 5.2$

k_m = mean rate constants for mice in reciprocal minutes

k_r = mean rate constants for rats in reciprocal minutes

Figure 1

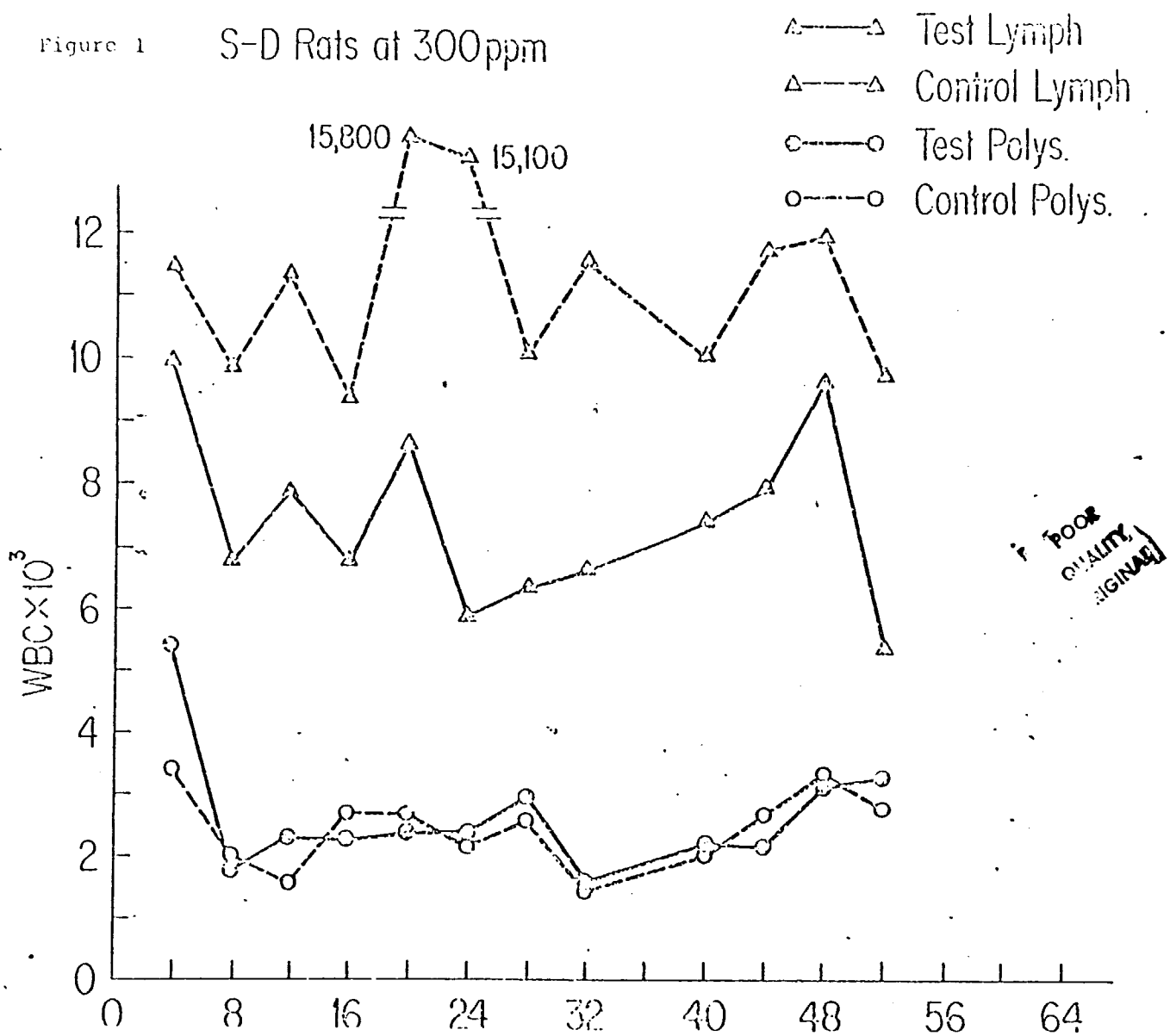
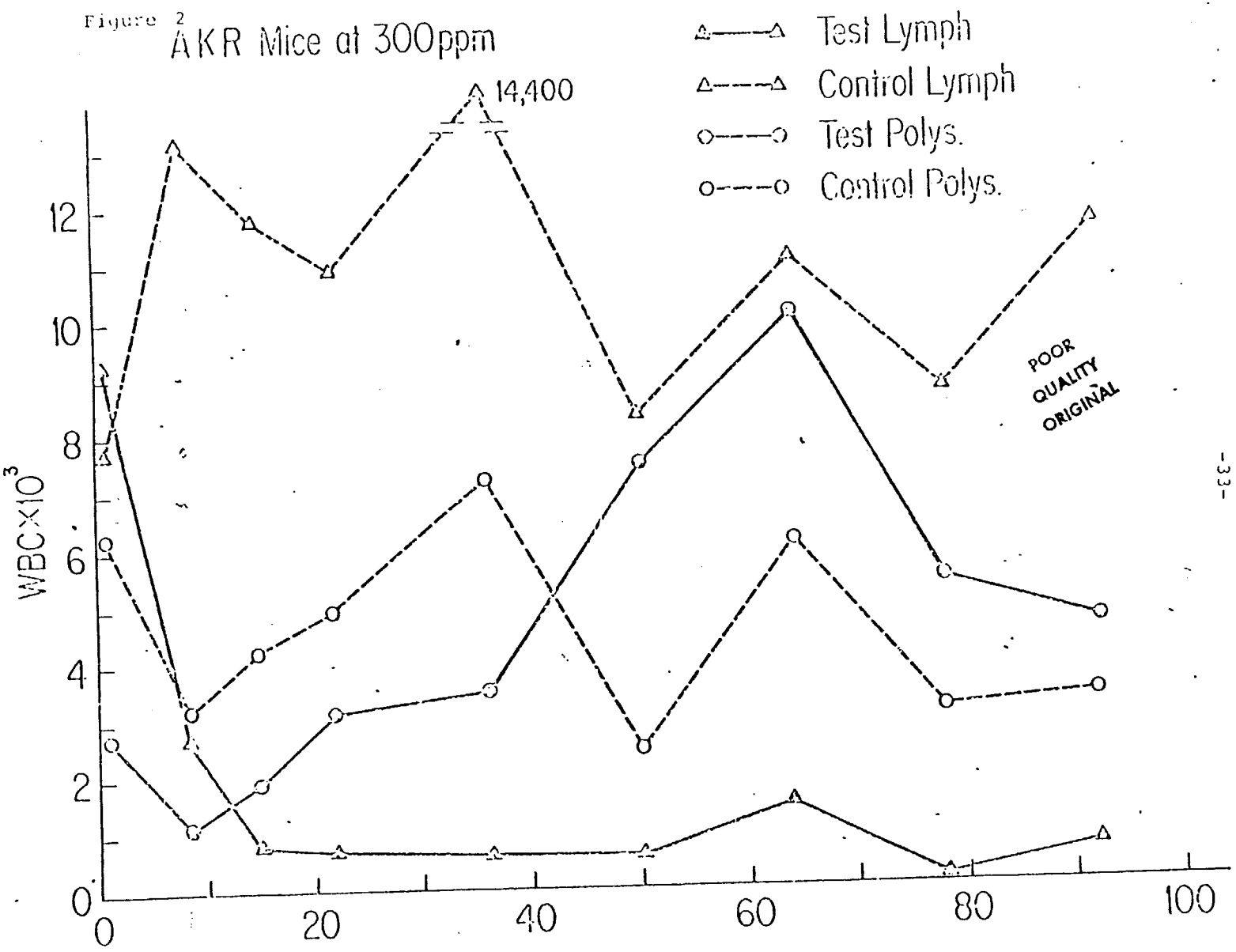


Figure 2


AKR Mice at 300ppm
Test Lymph
Control Lymph
Test Polys.
Control Polys.
14,400
WBC×10³
0
2
4
6
8
10
12
0
20
40
60
80
100
POOR QUALITY ORIGINAL

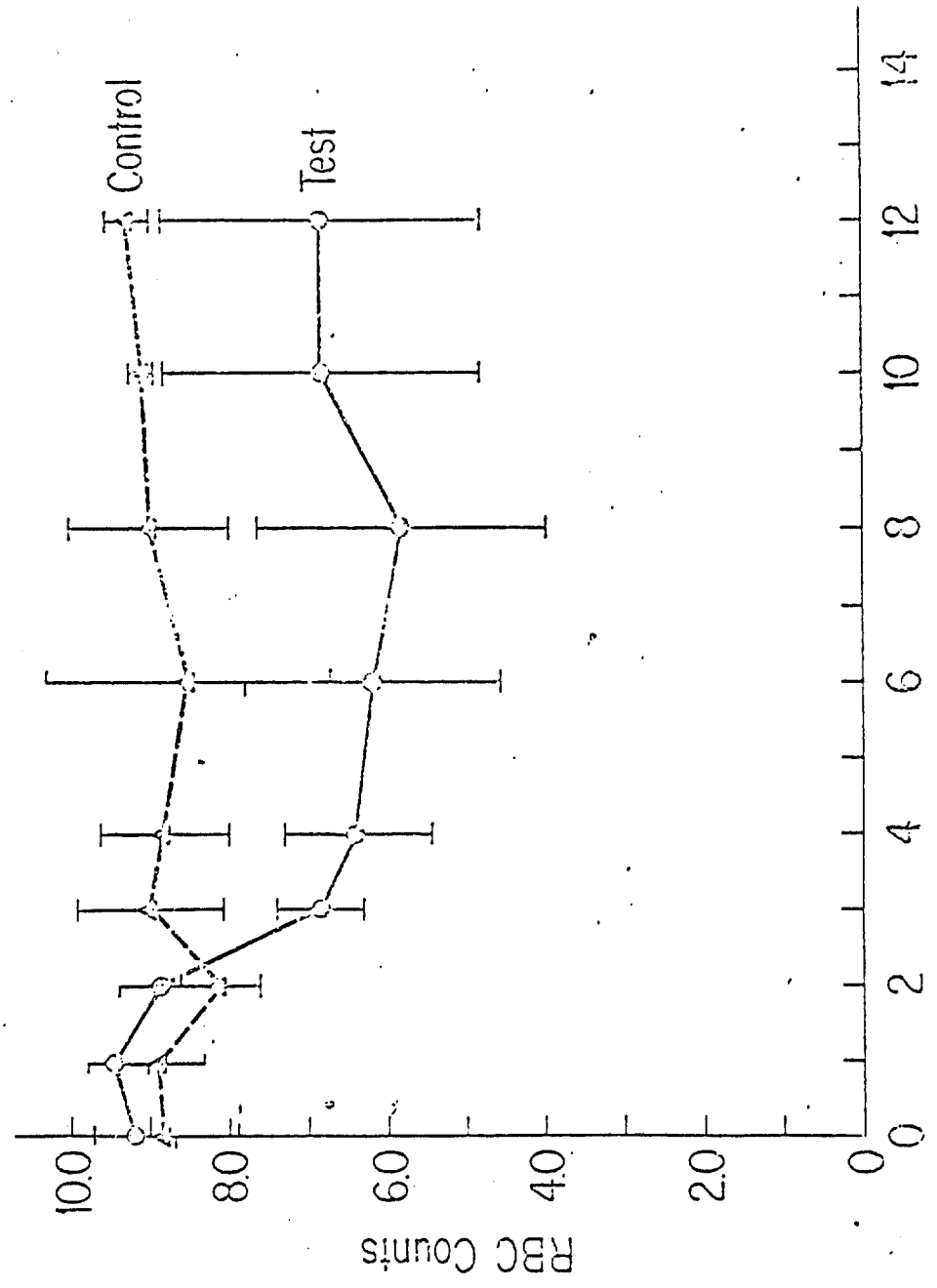

RBC of AKR Mice at 300 ppm
Control
Test
RBC Counts
10.0
8.0
6.0
4.0
2.0
0
0
2
4
6
8
10
12
14

Figure 3

Figure 4

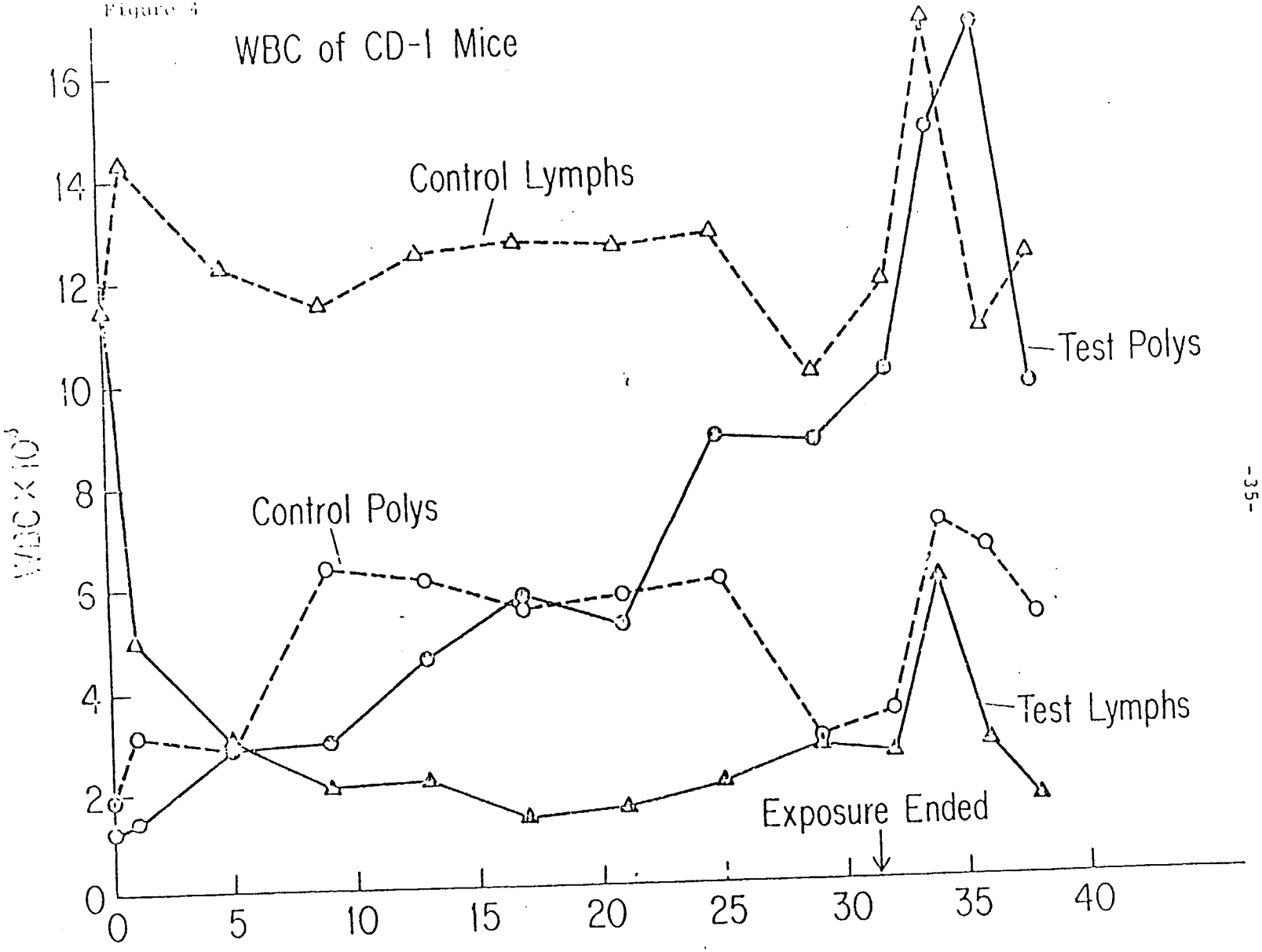
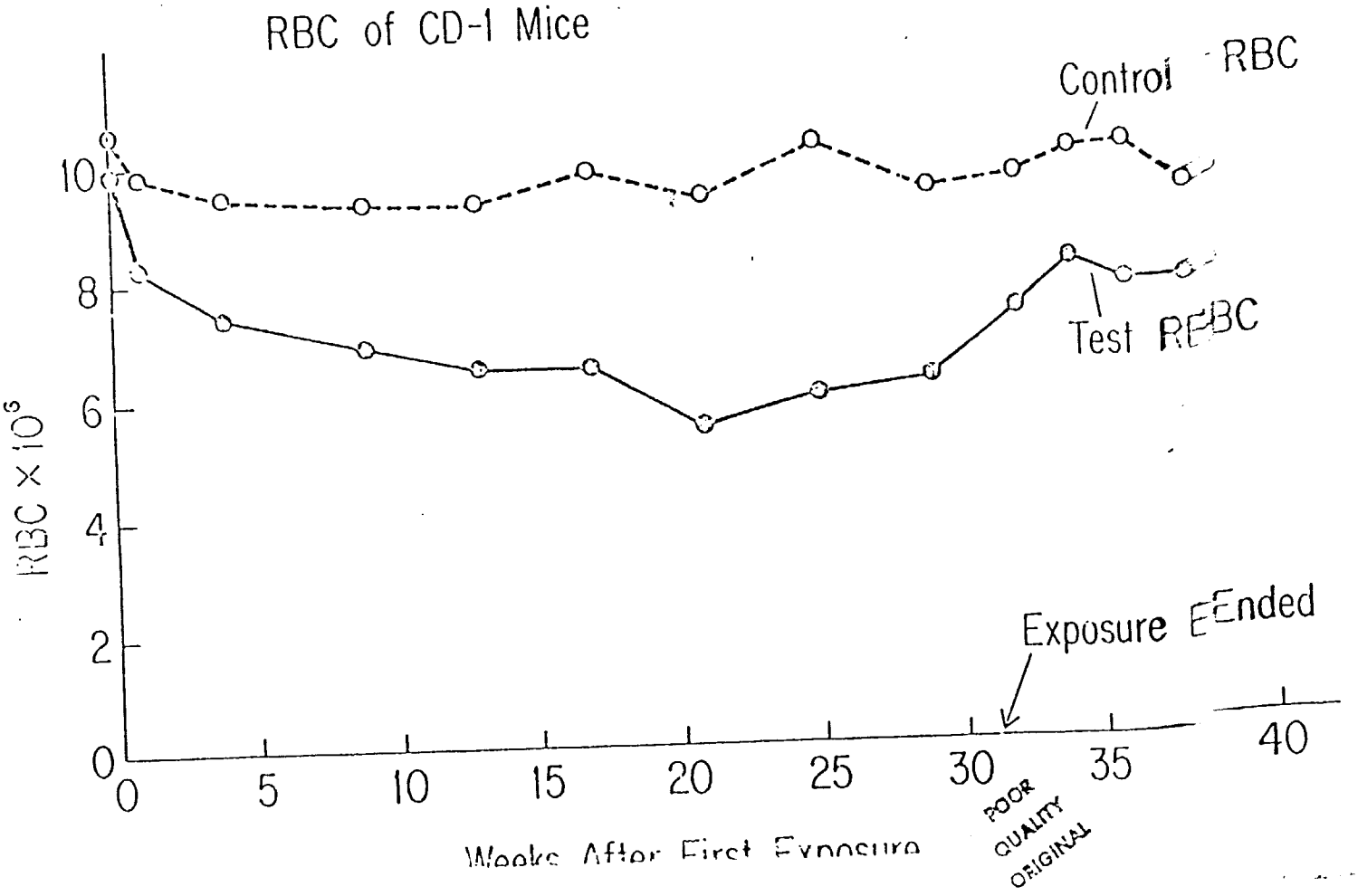

WBC of CD-1 Mice
Control Lymphs
Test Polys
Control Polys
Test Lymphs
Exposure Ended
WBC x 10³
0
2
4
6
8
10
12
14
16
0
5
10
15
20
25
30
35
40

Figure 5


RBC of CD-1 Mice
Control RBC
Test RBC
RBC × 10⁶
0
2
4
6
8
10
0
5
10
15
20
25
30
35
40
Exposure Ended
Weeks After First Exposure
POOR QUALITY ORIGINAL

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Barbara J. Price
Vice President
Health, Environment & Safety
Phillips Petroleum Company
Bartlesville, Oklahoma 74004

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAY 0 8 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and **refer to the reverse side of this page for "EPA Information Requests"** .

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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan
Risk Analysis Branch

Enclosure

12578A

H

Triage of 8(e) Submissions

Date sent to triage: 12/14/95

NON-CAP CAP

Submission number: 12578A

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

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entire document: 0 (1) 2 **pages** 1 **pages** 1, 2, tabs

Notes:

Contractor reviewer : LPS **Date:** 4/14/95

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # 8EHQ- 0992 -12578 SEQ. A

TYPE: (INT.) SUPP FLWP

SUBMITTER NAME: Phillips Petroleum Company

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 08/24/92 OTS DATE: 09/02/92 CSRAD DATE: 03/07/95

CHEMICAL NAME: Benzene

CAS# 71-43-2

INFORMATION TYPE:		P	F	C
0201	ONCO (HUMAN)	01	02	04
(0202)	ONCO (ANIMAL)	01	(02)	04
0203	CELL TRANS (IN VITRO)	01	02	04
0204	MUTA (IN VITRO)	01	02	04
0205	MUTA (IN VIVO)	01	02	04
0206	REPRO/TERATO (HUMAN)	01	02	04
0207	REPRO/TERATO (ANIMAL)	01	02	04
0208	NEURO (HUMAN)	01	02	04
0209	NEURO (ANIMAL)	01	02	04
0210	ACUTE TOX. (HUMAN)	01	02	04
0211	CHR. TOX. (HUMAN)	01	02	04
0212	ACUTE TOX. (ANIMAL)	01	02	04
0213	SUB ACUTE TOX (ANIMAL)	01	02	04
0214	SUB CHRONIC TOX (ANIMAL)	01	02	04
(0215)	CHRONIC TOX (ANIMAL)	01	(02)	04

INFORMATION TYPE:		P	F	C
0216	EPI/CLIN	01	02	04
0217	HUMAN EXPOS (PROD CONTAM)	01	02	04
0218	HUMAN EXPOS (ACCIDENTAL)	01	02	04
0219	HUMAN EXPOS (MONITORING)	01	02	04
0220	ECO/AQUA TOX	01	02	04
0221	ENV. OCCC/REL/FATE	01	02	04
0222	EMER INCI OF ENV CONTAM	01	02	04
0223	RESPONSE REQES'T DELAY	01	02	04
0224	PROD/COMP/CHEM ID	01	02	04
0225	REPORTING RATIONALE	01	02	04
0226	CONFIDENTIAL	01	02	04
0227	ALLERG (HUMAN)	01	02	04
0228	ALLERG (ANIMAL)	01	02	04
(0229)	METAB/PHARMACO (ANIMAL)	01	(02)	04
0230	METAB/PHARMACO (HUMAN)	01	02	04

INFORMATION TYPE:		P	F	C
0241	IMMUNO (ANIMAL)	01	02	04
0242	IMMUNO (HUMAN)	01	02	04
0243	CHEM/PHYS PROP	01	02	04
0244	CLASTO (IN VITRO)	01	02	04
(0245)	CLASTO (ANIMAL)	01	(02)	04
0246	CLASTO (HUMAN)	01	02	04
0247	DNA DAM/REPAIR	01	02	04
0248	PROD/USE/PROC	01	02	04
0251	MSDS	01	02	04
0299	OTHER	01	02	04

Ctox

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES)	YES (DROP/REFER)	RAT	LOW		
CAS SR	NO	NO (CONTINUE)	MUS	MED		
	IN TRANSIN	REVIEW		(HIGH)		

COMMENTS: Rats and mice were exposed by inhalation to benzene for 6 hours/day & 5d/week for 99 weeks at 100 & 300 ppm. Main adverse effects were on blood & hematopoietic tissues. These changes were more pronounced at 300 ppm exposure and included leukopenia, increased hemosiderin pigments of spleen and bone marrow hypoplasia. Red cells glutathione along with reduced red blood cells. No histopathology provided.

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # SEHQ- 1092 -12584 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Elf Atochem North America, Inc.

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL. ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
0510 REFER TO CHEMICAL SCREENING
(0511) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER/CUSTOMERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 09/11/92 OTS DATE: 10/06/92 CSRAD DATE: 03/07/95

CHEMICAL NAME: TBTO Bis(tri-n-butyltin)oxide

CASE: 56-35-9

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
(0202)	ONCO (ANIMAL)	01 (02) 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
(0207)	REPRO/TERATO (ANIMAL)	01 (02) 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
(0213)	SUB ACUTE TOX (ANIMAL)	01 (02) 04
(0214)	SUB CHRONIC TOX (ANIMAL)	01 (02) 04
(0215)	CHRONIC TOX (ANIMAL)	01 (02) 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
(0230)	METAB/PHARMACO (ANIMAL)	01 (02) 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
(0241)	IMMUNO (ANIMAL)	01 (02) 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
(0248)	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

[redacted]

TSCA INVENTORY	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES)	YES (DROP/REFER)	RAT	LOW	Molluscicide	
CAS SR	NO	NO (CONTINUE)		MED		
	IN INVENTORY	RAJ'S R		(HIGH)		

COMMENTS: Rats (Wistar) recieved TBTO at dietary does of 0, 5, 20, 80 and 320 mg/kg/(320 mg for 6 weeks) for 4 and 6 weeks. Treatment produced effects in organs including thymus, spleen, liver, thyroid and pituitary at 320 and 80 mg/kg. Hematologic changes included decreased leucocytes, hemoglobin and hematocrit values. Microscopic lesions observed included thymic and spleen atrophy, multifocal necrosis of liver parenchyma, flattening of the epithelial lining of thyroid follicles and decreased TSH immunoreactive cells in pituitary. The NOAEL was 20 mg/kg.

Table 9. Summary of functional assessment of specific and nonspecific resistance after short-term and long-term exposure in the rat

	6 weeks[a]		4-6 months			15-17 months		
Dietary concentration (mg/kg)	20	80	0.5	5	50	0.5	5	50
Thymus-dependent immunity								
T.spiralis infection: expulsion of adult worms	↓	↓↓						
resistance to muscle larvae	↓	↓↓	-	↓	↓↓	-	↓	↓↓
IgE response	↓	↓	-	↓	↓↓	-	↓	↓
Delayed type hypersensitivity to ovalbumin and tuberculin	↓	↓↓	-	-	-	-	-	-
IgM and IgG response to *T.spiralis* and ovalbumin	-	-	-	-	-	-	-	-
IgG response to sheep red blood cells	-	↓				-	-	-
T-mitogen response, thymus	↓	↓↓	-	-	↓			
T-mitogen response, spleen	-	↓	-	-	-	-	-	-
Nonspecific resistance								
L.monocytogenes infection, splenic clearance	↓	↓↓	-	-	↓	-	-	↓
Natural cell-mediated cytotoxicity, peritoneal macrophages	↓	↓	-	-	-			
Natural cell-mediated cytotoxicity, splenic NK cells	-	↓	-	-	↓	↓	↓	↓

[a] From Vos *et al.*, 1984.

- no suppression; ↓ slight to moderate suppression; ↓↓ strong suppression

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # 8EHQ- 0992-12578 SEQ. A

TYPE: (INT.) SUPP FLWP

SUBMITTER NAME: Phillips Petroleum Company

SUB. DATE: 08/24/92 OTS DATE: 09/02/92 CSRAD DATE: 03/07/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/USERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:

CAS#
71-43-2

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
(0202)	ONCO (ANIMAL)	01 (02) 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
(0215)	CHRONIC TOX (ANIMAL)	01 (02) 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQES: DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
(0239)	METAB/PHARMACO (ANIMAL)	01 (02) 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
(0245)	CLASTO (ANIMAL)	01 (02) 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

Onco

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES)	YES (DROP/REFER)	RAT	(LOW)		
CAS SR	NO	NO (CONTINUE)	mus	(MED)		
	UNKNOWN	REFER		HIGH		

(ND)

COMMENTS

12578A

L/L/M/ND

Carcinogenicity in the Sprague Dawley rat is of low concern. Male rats were exposed via inhalation to 0 or 300 ppm benzene (27 controls and 45 exposed) for 6 hours/day, 5 days/week for life. Median survival time was decreased in the exposed rats. Hematological effects were: significant leukopenia due to selective decreases in lymphocyte levels, and slight anemia. Histopathology showed significantly increased incidence of hemosiderin pigments in the spleen and increased incidence of fatty changes of the bone marrow. There was no evidence of leukemia or lymphomas. An additional experiment was in progress involving 40 mice/group exposed to 0 or 100 ppm using the same exposure protocol as for 300 ppm. Histological analysis at 100 ppm was not complete, but one treated rat died due to chronic myelogenous leukemia. One treated rat that had not died also showed evidence of chronic myelogenous leukemia, but this leukemia had not been observed in any control rats. Although results at the low concentration were not complete, this study was rated low concern based on the absence of carcinogenic findings at the high concentration. However, it is unclear how complete the histopathological analysis was.

Inhalation carcinogenicity in the AKR mouse is of low concern. Groups of 60 male mice were exposed to 0 or 300 ppm for 6 hours/day, 5 days/week for life; separate testing was conducted with 50 mice/group exposed to 100 ppm and concurrent controls using the same exposure protocol. Survival time was markedly reduced at 300 ppm, but not at 100 ppm. No mice survived exposure to 300 ppm for more than 28 weeks, and severe weight loss was observed at this level. Lymphocytopenia and anemia were observed with concentration-related severity. The incidence of malignant lymphoma was lower at 300 ppm (2%) than in the control mice (91%), due to the high background rate in this strain and the median survival time in the exposed mice being shorter than the time to the first tumor in the controls. However, cytogenetic analysis showed increased aneuploidy of bone marrow cells from treated animals. At 100 ppm, the incidence of malignant lymphoma was comparable in the treated group (29/49) and the controls (24/50). Noncancer histological effects observed were increased incidences of hemosiderin pigments in the spleen and bone marrow hypoplasia at both treatment levels. This study is limited by the incomplete identification of the organs that underwent histopathological analysis.

Inhalation carcinogenicity in the C-57 B1 mouse is of medium concern. Groups of 40 male mice were exposed to 0 or 300 ppm for 6 hours/day, 5 days/week for life. Median survival time in exposed mice was 49 weeks, versus 83 weeks for the controls, and the exposed mice showed decreased weight gain compared to the controls for the duration of the study. Hematological findings in exposed mice were lymphocytopenia, anemia, granulocytosis, and hypoplastic bone

marrow. Malignant lymphoma was significantly increased in exposed mice (9/40) versus the controls (2/40). In addition, 13/31 exposed mice showed bone marrow hyperplasia and 15/31 had spleen hyperplasia, compared with no cases of bone marrow hyperplasia and 2/38 of spleen hyperplasia in the controls. This study is limited by the incomplete identification of the organs that underwent histopathological analysis.

Inhalation carcinogenicity in the CD-1 mouse is not determined, due to incomplete histological data for the treated group and no reported histological data for the control group. Groups of 40 male mice were exposed to 0 or 300 ppm for 6 hours/day, 5 days/week for life. Median survival time in exposed mice was about 60% that of the controls, and the exposed mice showed decreased weight gain compared to the controls for the duration of the study. Hematological findings in exposed mice were lymphocytopenia, anemia, and granulocytosis. Histological analysis was not complete, but histology was described for three treated mice, one dying of chronic myelogenous leukemia, one dying of acute myelogenous leukemia, and one diagnosed as having granulocytic hyperplasia, which was considered a pre-myelogenous leukemic state.